Intron retention in mRNA encoding ancillary subunit of insect voltage-gated sodium channel modulates channel expression, gating regulation and drug sensitivity.

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Résumé en anglais	Insect voltage-gated sodium (Nav) channels are formed by a well-known pore-forming α-subunit encoded by para-like gene and ancillary subunits related to TipE from the mutation "temperature-induced-paralysis locus E." The role of these ancillary subunits in the modulation of biophysical and pharmacological properties of Na(+) currents are not enough documented. The unique neuronal ancillary subunit TipE-homologous protein 1 of Drosophila melanogaster (DmTEH1) strongly enhances the expression of insect Nav channels when heterologously expressed in Xenopus oocytes. Here we report the cloning and functional expression of two neuronal DmTEH1-homologs of the cockroach, Periplaneta americana, PaTEH1A and PaTEH1B, encoded by a single bicistronic gene. In PaTEH1B, the second exon encoding the last 11-amino-acid residues of PaTEH1A is shifted to 3'UTR by the retention of a 96-bp intron-containing coding-message, thus generating a new C-terminal end. We investigated the gating and pharmacological properties of the Drosophila Nav channel variant (DmNav1-1) co-expressed with DmTEH1, PaTEH1A, PaTEH1B or a truncated mutant PaTEH1Δ(270-280) in Xenopus oocytes. PaTEH1B caused a 2.2-fold current density decrease, concomitant with an equivalent α-subunit incorporation decrease in the plasma membrane, compared to PaTEH1A and PaTEH1Δ(270-280). PaTEH1B positively shifted the voltage-dependences of activation and slow inactivation of DmNav1-1 channels to more positive potentials compared to PaTEH1A, suggesting that the C-terminal end of both proteins may influence the function of the voltage-sensor and the pore of Nav channel. Interestingly, our findings showed that the sensitivity of DmNav1-1 channels to lidocaine and to the pyrazoline-type insecticide metabolite DCJW depends on associated TEH1-like subunits. In conclusion, our work demonstrates for the first time that density, gating and pharmacological properties of Nav channels expressed in Xenopus oocytes can be modulated by an intron retention process in the transcription of the neuronal TEH1-like ancillary subunits of P. americana.
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